The opinion in support of the decision being entered today is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte YEN CHOO, AARON KLUG, and MARK ISALAN

Appeal 2007-0743
Application 09/424,482
Technology Center 1600

Decided: August 23, 2007

Before TONI R. SCHEINER, DONALD E. ADAMS, and NANCY J. LINCK, *Administrative Patent Judges*.

LINCK, *Administrative Patent Judge*.

ADAMS, *Administrative Patent Judge*, dissenting.

DECISION ON APPEAL

This is a 35 U.S.C. § 134 appeal in the above-referenced case.[1]

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] The application was filed on February 29, 2000. The real party in interest is Gendaq, Ltd., a wholly owned subsidiary of Sangamo Biosciences, Inc.

STATEMENT OF THE CASE

"The present claims are directed to libraries of zinc finger proteins in which positions 2 and 6 of adjacent zinc fingers are at least partially randomized." (Appellants' Revised Brief Under 37 C.F.R. § 41.37 (received March 20, 2006) (hereafter "Br.") 3.) According to the Specification,

> Many DNA-binding proteins contain independently folded domains for the recognition of DNA, and these domains in turn belong to a large number of structural families, such as the leucine zipper, the "helix-turn-helix" and zinc finger families.
>
> Despite the great variety of structural domains, the specificity of the interactions observed to date between protein and DNA most often derives from the complementarity of the surfaces of a protein α-helix and the major groove of DNA [Klug, (1993) Gene 135:83-92]. In light of the recurring physical interaction of α-helix and major groove, the tantalising possibility arises that the contacts between particular amino acids and DNA bases could be described by a simple set of rules; in effect a stereochemical recognition code which relates protein primary structure to binding-site sequence preference.

(Specification (hereafter "Spec.") 1.[2]) According to the Specification, no prior art method has succeeded in providing a complete code. (*Id.* at 2.)

Appellants based their library on the understanding that "zinc finger binding sites are determined by overlapping 4 bp subsites, and that sequence-specificity at the boundary between subsites arises from synergy between adjacent fingers." (*Id.* at 2-3.) Knowledge of this overlap resulted in Appellants' claimed invention which "provides a zinc finger polypeptide

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[2] The numbers referenced for the Specification are those typed at the top of the pages and not the hand-written numbers at the bottom.

library in which each polypeptide comprises more than one zinc finger which has been at least partially randomised." (*Id.* at 3.) Consistent with their knowledge of this overlap, Appellants originally claimed: "A zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger and wherein each polypeptide has been at least partially randomized such that the randomization extends to cover the overlap of a single pair of zinc fingers." (Spec. 39.)

The claimed subject matter is reflected in representative claims 1 and 30, claims which restrict randomization at position 2 or 6 respectively. These claims now read:[3]

> 1. A zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger comprising amino acid positions -1 to + 9 with position 1 representing the first amino acid of an alpha-helix and wherein each polypeptide has been at least partially randomised such that the randomisation extends to cover at least positions 6 and 2 of adjacent first and second fingers, respectively, wherein the randomisation of amino acid residues at position 2 is restricted to amino acids selected from the group consisting of D, A, R, Q, H, K, S, and N.
>
> 30. A zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger comprising amino acid positions -1 to + 9 with position 1 representing the first amino acid of an alpha-helix and wherein each polypeptide has been at least partially randomised such that the randomisation extends to cover at least positions 6 and 2 of adjacent first and second fingers, respectively, wherein the randomisation of amino acid at position 6 is restricted to amino acids selected from the group consisting of R, Q, V, A, E, K, N, and T.

[3] Claims 1 and 30 are the only independent claims before us.

The Examiner has rejected claims 1-2, 6-7, and 27-34 under 35 U.S.C. § 103(a) over the following references:

Greisman, H.A. "*A general strategy for selecting high-affinity zinc finger proteins for diverse DNA target sites*," 275 Science 657-61 (January 31, 1997) (hereafter "Greisman").

Choo, Y., "*Designing DNA-binding proteins on the surface of filamentous phage*", 6 Current Opinion in Biotechnology 431-36 (1995) (hereafter "Choo '95").

The Examiner also has rejected claims 1-2, 6, and 27-34 under 35 U.S.C. § 112, ¶ 1, for lack of written description.[4]

In addition to the above-cited references, the following additional references show the state of the art and thus the level of skill in the art:[5]

Choo & Klug, *Toward a code for the interactions of zinc fingers with DNA: selection of randomized zinc fingers displayed on phage*, 91 Proc. Natl. Sci. USA 11163-11167 (1994) (hereafter "Choo '94-1") (cited in Choo '95 and relied upon by Appellants (Br. 7 n.1 & accompanying text)).

Choo & Klug, *Selection of DNA binding sites for zinc fingers using rationally randomized DNA reveals coded interactions*, 91 Proc. Natl. Sci. USA 11168-11172 (1994) (hereafter "Choo '94-2") (cited in Choo '95).

Choo & Klug, *Physical basis of a protein-DNA recognition code*, 7 Current Opinion in Structural Biology 117-25 (Feb. 1997) (hereafter "Choo '97").

Isalan, Choo and Klug, *Synergy between adjacent zinc fingers in sequence-specific DNA recognition*, 94 Proc. Natl. Acad. Sci. USA 5617-21 (May 1997) (hereafter "Isalan").

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[4] On appeal, the Examiner withdrew a § 112, ¶ 2 rejection of claims 6 and 32 (Answer 2) and admitted claim 7 should not have been rejected under § 112, ¶ 1 (Answer 3).

[5] All of these references describe one or more of the inventors' own prior art work and were cited to the Office by the inventors. (*See* Information Disclosure Statements received Nov. 23, 1999 and Dec. 31, 2001.) In addition, two were cited in Choo '95.

OBVIOUSNESS UNDER § 103(a)

The § 103(a) Issue

Appellants contend:

> [T]he cited references do not teach or suggest the groups of amino acids recited in independent claim 1 and claim 30 to which partial randomization of amino acids is restricted (D, A, R, Q, H, K, S, and N, in claim 1 and R, Q, V, A, E, K, N, and T in claim 30). . . . Greisman teaches to randomize in such a manner as to allow any of sixteen amino acids at each position (footnote 15 of Greisman). . . . Choo ['95] does not explicitly disclose whether he restricted randomization to certain codons. However, reference to his earlier work [Choo '94-1] . . . shows that he, like Greisman, restricted randomization to sixteen amino acids.

(Br. 7-8.)

The Examiner responds:

> Greisman discloses at least at page 659, Fig. 3[A], the different zinc finger polypeptide[s] with random amino acid residues at position -1 up to position 6 . . . .
>
> Appellants recognized that Greisman teaches random amino acids with any of sixteen amino acids at each position omitting Trp, Phe, Tyr and Cys. [Note the instant claim does not also recite these residues, unless of course this is the non-preferred residues]. It would be within the ordinary skill in the art at the time the invention was made to pick and choose from the known available sixteen amino acids disclosed by Greisman, the ones that can combine to form the instant library. Greisman discloses, or at least suggests, from the 16 amino acids the random species at each position[] of the zinc finger as shown at Fig. 3. . . . Choo ['95] discloses that combinations or en bloc residues of zinc fingers can be random. Therefore, the combined teachings of the prior art would have led one having ordinary skill in the art at the time the invention was made to the instant random library. . . .
>
> . . . .

> Appellants state that restricting the sets of amino acids at positions 2 and 6 is optimal . . . .
>
> In reply, neither claim 1 nor claim 30 restricts the sets of amino acids at positions 2 and 6. . . . Furthermore, the specification does not disclose that the restricted set of amino acids result[s] in an optimal library. Rather, [it discloses] that the library is screened for the residues that bind[] to the DNA target site. Be [that] as it may, optimization of a given parameter is within the ordinary skill in the art.

(Examiner's Answer (mailed June 1, 2006) (hereafter "Answer") 9-12 (first bracketed material in original).)

In response, Appellants point out:

> [T]he zinc finger proteins whose sequences are shown in Fig. 3A of Greisman are not themselves a library of zinc finger proteins but rather eight individual clones from a library of zinc finger proteins (see, e.g., Greisman, p. 658, paragraph bridging cols. 1 and 2). . . . The actual physical zinc finger proteins existed as individual isolates and together with other zinc finger proteins as a large library, but not together as a library consisting only of the zinc finger proteins whose sequences are shown in Fig. 3A. . . .
>
> Even if . . . it were assumed that the sequences of zinc finger proteins shown in Fig. 3A of Greisman were a library of zinc finger proteins, the diversity required by claim[] 1 . . . would still not be present. Claim 1 specifies inter alia that . . . randomization at position 2 is restricted to amino acids selected from the group D, A, R, Q, H, K, S and N. However, the randomization at position 2 is not so restricted in the zinc finger proteins shown in Fig. 3A. For example, position 2 of finger 1 contains a T in some of the sequences shown in Fig. 3A, a residue not allowed by the recited Markush group in claim 1.

(Reply Br. 4-5.)

With respect to the Examiner's position that it would have been obvious to optimize the amino acids, Appellants respond:

> [S]election of subsets of amino acids for randomization to produce a library of zinc finger protein is not a continuous linear parameter that allows simple interpolations [like the situation in *In re Aller*]. Each of the amino acids is different, and the effect of its presence or absence at a given zinc finger position on the binding characteristics of a library of zinc finger proteins was unpredictable. Thus, selection of a set of amino acids to improve binding characteristics of a zinc finger protein library is not comparable to selecting a temperature or concentration of acid to conduct a chemical process.
>
> Moreover, a prima facie case of obviousness based on optimization of ranges can be rebutted by showing that the art in any material respect teaches away from the claimed invention (*In re Geisler*, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997)). Here, as discussed above, the art teaches that more different amino acids than were used by Greisman, not fewer (as claimed), would be desirable. The suggestion that more rather than fewer amino acids are desirable would have taught away from selecting a subset of the sixteen amino acids of Greisman.

(Reply Br. 8.)

We frame the § 103(a) issue: Would the zinc finger library of claims 1 and 30, including randomization in positions 6 and 2 of adjacent first and second fingers and restricted randomization in position 2 (claim 1) or 6 (claim 30), have been obvious to a skilled artisan, in view of Greisman's and Choo '95's teachings?

Findings of Fact Relating to Obviousness

Claim Interpretation

1. Giving the claim its broadest reasonable interpretation in light of the Specification, "library" requires two polypeptides. (Spec. 3 ("library is used . . . to denote a collection of polypeptides").

2. "Randomization," as used in the claims and defined in the specification, "refers to the variation of the sequence of the polypeptides which comprise the library, such that various amino acids may be present at any given position in different polypeptides" (Spec. 6); but is not limited to simultaneous randomization on adjacent zinc fingers.

3. With respect to "each polypeptide," claim 1 requires randomization at "positions 6 and 2 of adjacent first and second fingers, respectively," and restriction of randomization at position 2 to "D, A, R, Q, H, K, S, and N."

4. Claim 30 requires randomization at "positions 6 and 2 of adjacent first and second fingers, respectively," and restriction of randomization at position 6 to "R, Q, V, A, E, K, N, and T."

5. Thus, claims 1 and 30 require a library of 2 polypeptides comprising 2 adjacent zinc fingers that have been partially randomized at positions 6 and 2, with randomization restricted to 8 of the 20 possible amino acids at a single position, i.e., position 2 (claim 1) or at position 6 (claim 30).

The Cited Prior Art

6. Greisman recognizes "the overlapping base contacts that can occur at the junction of neighboring subsites," i.e., positions 2 and 6 (Fig. 1B & Fig. 2 caption) and designs his strategy accordingly. (*Id.*)

7. Greisman identifies zinc finger proteins with high affinity for DNA target sites by recognizing "context-dependent interactions are important for zinc finger-DNA recognition" and "ensur[ing] that the new fingers are always selected in a relevant structural context." (Greisman 657, cols. 2, 3.)

8. Greisman's strategy involves a "method . . . for selecting DNA-binding proteins," i.e., zinc finger proteins, by "adding and optimizing one finger at a time." (Greisman 657 (abstract)).

9. Greisman uses the Zif268 structure, a known zinc finger structure, as a starting point and then "randomize[s] six potential base-contacting positions in each finger," i.e., positions -1, 1, 2, 3, 5, and 6 (Greisman 657, col. 2 & 658 (Fig. 1)) using 16 amino acids and omitting 4 amino acids also omitted by Appellants. (Greisman note 15 & accompanying text.)

10. Greisman's Fig. 2 illustrates their "protocol that successively selects finger 1, finger 2, and finger 3 to create a new zinc finger protein." (Greisman 658 (Fig. 2 caption).)

11. Greisman begins with two known zinc fingers, Zif1 and Zif2 (wild-type Zif268 fingers) "to position the library of randomized fingers over the target site," and then adds third zinc fingers from the randomized finger library, creating a "finger 1 library," so called because this step selects potential finger 1 candidates for the ultimate 3-finger proteins. (Greisman 657, col. 3 & 658 (Fig. 2A).) From these potential "finger 1" candidates, Greisman selects and amplifies 3-finger peptides that bind to identified DNA binding sites, e.g., the TATA box. (*See id.*)

12. In step two, Greisman removes Zif1 from the 3-finger peptides but retains two of the fingers, Zif2 and select "finger 1," and then ligates a "randomized finger 2 cassette" to these 2-finger peptides, again creating a

library from which 3-finger peptides that bind to identified DNA binding sites are selected and amplified. (*Id.* at 657, col. 3 & 658 (Fig. 2B).)

13. Finally, in step three, Greisman removes Zif2, leaving randomized fingers 1 and 2 that have been selected for their binding affinities, adds a "randomized finger 3 cassette," and optimizes the final 3-zinc finger proteins.

14. Greisman's protocol "actually was designed so that a *sublibrary of successful zinc finger sequences* could be carried over from one selection step (Fig. 2, A or B) to the next" and the final third step "then selects for combinations of fingers that work well together." (Greisman 660 n. 16 (emphasis added); see also Greisman 660 n. 19 ("Each set of proteins exhibits a clear gradient of sequencing diversity across the three fingers (Fig. 3)").)

15. Greisman's sublibrary of successful zinc finger sequences from step 3 that bind to the TATA box are shown in Fig. 3A. (Greisman 659; FFs 10-14.)

16. One result of Greisman's strategy is a group of "new zinc finger proteins that recognize . . . the TATA box." (Fig. 3A & caption.) Fig. 3A discloses the amino acid sequences for eight new 3-finger proteins that were selected from the third step library based on their ability to bind to the TATA box. (*Id.*; FFs 10-15.)

17. In each of the eight new zinc finger proteins that bind to the TATA box, Greisman discloses randomized amino acid sequences for Fingers 1, 2, and 3 at positions 2 and 6. (Greisman 659 (Fig. 3A).)

18. Further, in each of Greisman's eight new zinc finger proteins, all the randomized amino acids in position 6 are those permitted by claim 30;

and in position 2, eleven of the amino acids (out of twenty-four) are those permitted by claim 1. (Greisman 659 (Fig. 3A; *see also* Answer 10).)

19. Greisman's sublibrary includes at least two polypeptides satisfying the restricted randomization for both positions 2 and 6. (Fig. 3A (6^{th} & 7^{th} clones, fingers 2 and 3).) In fact, Greisman "overexpressed" the 6^{th} clone and used it for binding studies. (*See* Fig. 3 legend.)

20. Based on their binding potential, one of ordinary skill in the art would recognize the value of using Greisman's select zinc finger proteins (identified in Fig. 3A) in a zinc finger library for a number of purposes, including as a starting point for further selection or "to allow selection of proteins with four, five, or six fingers or to allow optimization of zinc fingers fused to other DNA-binding domains." (Greisman 659, col. 3.)

21. Since Greisman's sublibrary includes polypeptides that satisfy claim 1, to the extent Appellants' claimed amino acid selection has been optimized for position 2, one of ordinary skill in the art would have been motivated to optimize Greisman's selected zinc fingers through further randomization, coupled with binding experiments, such as those conducted by Greisman, with a reasonable likelihood of identifying amino acids with high affinity for DNA.

22. Choo '95 is also interested in identifying zinc fingers that bind to DNA and describes the physical basis of a possible protein-DNA recognition code, identifying the positions on the zinc fingers that make contact with the DNA, i.e., positions -1, 3, and 6 on one strand and position 2 on the second strand. (Choo '95, 432.)

23. Following a description of prior art publications, Choo '95 states: "From the large database of results, elements of a code can be deduced that

describe DNA recognition by zinc fingers." (Choo '95 at 432 (citing to Choo '94-2 for discussion of this code).)

24. Greisman and Choo '95 randomized to 16 amino acids, omitting Cys, Phe, Tyr, and Trp to avoid stop codons (*see* Reply Br. 8); of these 16, Appellants randomized to 8 with respect to position 2 or 6, also omitting Cys, Phe, Tyr, and Trp. (See claims 1 and 30.)

Additional Findings of Fact

25. Zinc finger binding motifs are structures "well known to those in the art and defined in" a number of references. (Spec. 14.)

26. "Detailed methodology for phage display is known in the art and set forth in" a number of references, and "[v]ector systems and kits for phage display are available commercially." (Spec. 6.)

27. A number of alternative methods for generating zinc finger libraries with randomized amino acids at positions -1 through 6 were known to those skilled in the art at the time the invention was made. (*See, e.g.*, Greisman at 657-58 & nn. 15-16; Choo '95 at 432-34.)

28. Randomized zinc finger libraries were known in the art, and DNA recognition sites on the fingers (positions -1 to 6) were also known. (*See, e.g.,* Greisman *passim*; Choo '95, 431-32.)

29. Inter-finger "synergism," or "context-dependent interactions," due to overlapping 4 bp subsites was well recognized by those skilled in the art. (*See, e.g.*, Greisman 657-58; Isalan 5620; Choo '97, 117.)

30. The cocrystal structures of a number of DNA-zinc finger complexes, including ones with zinc fingers Zif268 and Trk, are known, and the amino acids which bind to DNA have been identified as those at

positions -1, 3, and 6 on one finger and position 2 on the adjacent finger. (*See. e.g.*, Choo '94-1, 11166, col. 2; Choo '95, 432; Choo '97, 120 (Figs. 3 & 4); Isalan 5617; Choo '98, 2.)

31. With respect to these binding positions, it was also recognized that only certain amino acids are found at those positions. (*See, e.g.,* Choo '94-1, 11166, col. 2.)

32. The skilled artisan would have been motivated to optimize the amino acids on zinc finger proteins for a given DNA sequence and would have had a reasonable expectation of doing so, given the limited number of possible amino acids and the extensive guidance in the art. (FFs 25-31.)

Discussion of the § 103(a) Issue

Based on our findings and those of the Examiner, we conclude the invention claimed in claims 1 and 30 would have been obvious to one of ordinary skill in the art at the time the invention was made.

The skilled artisan's knowledge of zinc finger protein-DNA complexes is extensive. (FFs 6-31.) At the time the claimed invention was made, the basis for Appellants' invention, i.e., "synergism" or "context-dependent interactions" between position 6 on one finger and position 2 on an adjacent finger also was well recognized in the art. (FFs 6, 7, 22, 29 & 30.) Further, libraries of zinc finger proteins with at least two adjacent zinc fingers in which at least positions 2 and 6 were partially randomized to 16 amino acids (avoiding termination codons by not including Cys, Phe, Tyr, and Trp) were known. (FFs 6, 22, & 24; *see also* FFs 29 & 30.) Thus, such libraries were in the hands of the public to further refine and build upon.

Appellants now claim libraries of zinc finger proteins in which at least position 2 or 6 is partially randomized to 8 amino acids instead of 16, while

the remaining positions can be randomized to an unspecified number of amino acids. (Claims 1 and 30.) Thus, each claim would provide exclusivity for libraries that can be identical to those in the public domain, except for the restricted randomization in one position (limited to 8 amino acids rather than 16). In essence, Appellants are claiming a relatively large subgenus of the 16 amino acid genus in the prior art.

The situation here is similar to that in *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962) in which the prior art genus disclosed 20 compounds and a limited number of generic R groups in the formula, and applicant attempted to claim a species within that genus. The CCPA stated:

> [I]t is not the mere number of compounds in this limited class, . . . but, rather, the total circumstances involved, including such factors as the limited number of variations for R, only two alternatives for Y or Z, no alternatives for other ring positions, and a large unchanging parent structural nucleus. With these circumstances in mind, it is our opinion that Karrer has described to those with ordinary skill in this art each of the various permutations here involved as fully as if he had drawn each structural formula or had written each name.

Id. In this case, the prior art *fully describes* all 16 amino acids of the genus. Thus, as in *Petering*, one of ordinary skill in the art would "envisage *each member*" of the genus, including the 8 found in Appellants' subgenus. *Id.* (emphasis in original).

The fact that Appellants' 8 amino acids *may* bind better to DNA is not sufficient to render their claims patentable. The choice of amino acids in zinc fingers is a result-effective variable known to influence their binding to DNA. As such, one skilled in the art would have been motivated to optimize

that choice to improve binding using routine experimentation, i.e., techniques well known in the art. (FF 21.) *Cf. ,e.g., In re Boesch*, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) ("discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art"); *Merck & Co. v. Biocraft Labs. Inc.*, 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) ("predictable results" obtained through "routine procedures" not sufficient to support validity). (*See* FFs 11-14, 24, & 26-28; Answer 12.) Further, to the extent selection was "unpredictable," as Appellants argue (Reply Br. 8), unpredictability cannot be equated to nonobviousness when only a finite number of choices are available, as is the case here. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364, 82 USPQ2d 1321, 1332 (Fed. Cir. 2007) ("obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success").

Appellants do not disclose any unexpected results obtained by limiting position 2 or 6 to the amino acids in their subgenus. This is not surprising, since claims 1 and 30 are not limited to any specific DNA binding sequences. Optimization depends upon both the nature of the zinc finger amino acids and the DNA binding sequence. Thus, we conclude it would have been obvious to try to optimize the choice of amino acids from 16 to 8 using techniques known in the art, and success in doing so would have been anticipated.

Under *KSR*, it's now apparent "obvious to try" may be an appropriate test in more situations than we previously contemplated. When there is motivation

> to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007). This reasoning is applicable here. The "problem" facing those in the art was to determine what zinc finger amino acids would have high affinity for DNA out of the 16 amino acids randomized in the prior art, and there were a number of known methodologies available to do so. The skilled artisan would have had reason to use these methodologies to narrow the number of amino acids from 16 to 8, such as was done by Greisman, with the reasonable expectation of success. Thus, Appellants' elimination of 50% of the amino acids in a single position was "the product not of innovation but of ordinary skill and common sense," *id.*, leading us to conclude Appellants' claimed library of zinc finger polypeptides claimed in claims 1 and 30 is not patentable.

Further, with respect to claim 30, a library of at least two polypeptides in which position 6 is randomized to R, Q, V, A, E, K, N, or T is fully disclosed be Greisman. (*See* FFs 11-19.) While Appellants argue Greisman's Fig. 3A contains amino acids not permitted in position 2, they make no such argument with respect to position 6. Thus, we conclude claim 30 would have been obvious to the skilled artisan for this additional reason. *See, e.g., In re McDaniel*, 293 F.3d 1379, 1385, 63 USPQ2d 1462, 1466 (Fed. Cir. 2002) ("It is well settled that 'anticipation is the epitome of obviousness.'").

Appellants argue Greisman's zinc finger proteins disclosed in Fig. 3A are not a library. (Reply Br. 4.) In fact, Greisman teaches otherwise. (FFs 11-14.) Greisman creates a "sublibrary of successful zinc finger sequences" that bind to the TATA box. (FFs 14 & 16). This sublibrary meets the limitations of claim 30 and would have suggested that of claim 1 to the skilled artisan. (FFs 17-21; *see also* the discussion *supra* pp. 13-16.)

Appellants further argue Greisman "taught away from selecting a subset of the sixteen amino acids." (Reply Br. 8.) On the contrary, Greisman does exactly that, optimizing the zinc finger proteins disclosed in, e.g., Fig. 3A and thus limiting the number of amino acids in each position.

Dependent Claims 27, 28, 29, 33, and 34

Appellants separately argue claim 29 and claims 27, 28, 33, and 34.

Claim 29 is dependent upon claim 1 and restricts randomization at both positions 2 and 6 to those amino acids recited in claims 1 and 30.

Claims 27, 28, 33, and 34 are argued as a group. Thus, we select claim 27 as representative. Claim 27 restricts randomization at additional positions. It reads: "A library according to claim 1 wherein positions -1, 1, 2, 3, 5 and 6 of a first zinc finger and -1, 1, 2 and 3 of a second finger are randomized." These positions are those known to be "[k]ey base contacts." (*See, e.g.,* Greisman 658 (Fig. 1B & caption).)

We have considered Appellants' arguments relating to claims 27 and 29 and conclude their subject matter would have been obvious to one skilled in the art for the same reasons we so concluded with respect to claims 1 and 30. (*See "Discussion of the § 103(a) Issue," supra* pp. 13-16 & FFs 6-31.) Optimization of these binding sites would have been well within the level of skill in the art with routine experimentation.

WRITTEN DESCRIPTION UNDER § 112, ¶ 1

With respect to the written description issue, the Examiner finds the "specification, as originally filed, recites random *specific* amino acids for each of positions -1 to 6, particularly for the positions 6 and 2 pair," but does not support the language of claims 1 and 30, reciting random specific amino acids at position 2 or 6, respectively, but not at any other position. (Answer 3-4 (emphasis in original).)

In response, Appellants contend

> the specification states at page 11, lines 13-14: "It is not necessary for each finger to be randomized at each of the positions . . . given in Table 1. In addition, the specification provides a table of amino acids "*preferably selected*" to appear at each position (p. 11, lines 3-14, emphasis supplied). The table lists D, A, R, Q, H, K, S, and N for position 2 and R, Q, V, A, E, K, N, and T for position 6. By using the term "preferably selected," the specification conveys that position 2 is preferably occupied by D, A, R, Q, H, K, S, and N, but can less preferably be occupied by other amino acids. Likewise position 6 is preferably occupied by R, Q, V, A, E, K, N, T, but can also be occupied by other amino acids. . . . The table does not state that if one position is occupied by a preferred group of amino acids, then every other position must also be occupied by its preferred group of amino acids.

(Br. 5.)

In view of the above, we frame the written description issue: Does Appellants' Specification, as filed, contain a written description sufficient to show they had possession of the full scope of their claimed invention at the time the application was filed, as required by Federal Circuit precedent?

Findings of Fact Relating to § 112, ¶ 1

33. As originally filed, claim 1 read: "A zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger and wherein each polypeptide has been at least partially randomised such that the randomisation extends to cover the overlap of a single pair of zinc fingers." (Spec. 39.)

34. As originally filed, claim 7 read:

> A library according to any preceding claim, wherein the randomisation of amino acid residues is restricted such that the following amino acids may appear at the given positions:

Position	Possible Amino Acids
-1	R, Q, H, N, D, A, T
1	S, R, K, N
2	D, A, R, Q, H, K, S, N
3	H, N, S, T, V, A, D
5	I, T, K
6	R, Q, V, A, E, K, N, T

(Spec. 39.)

35. According to the Specification: "It is not necessary for each finger to be randomised at each of the positions." (Spec. 11.)

36. Claims 1 and 30 are of intermediate scope between originally-filed claims 1 and 7 (see Answer 6), and thus are supported by the originally-filed claims which are part of the specification.

Discussion of the Written Description Issue

With respect to claims 1 and 30, we find the written description requirement of § 112, ¶ 1, is satisfied. (FFs 33-36.) The Examiner does not provide any separate bases to support her written description rejection of

dependent claims 2, 6, 27-29, and 31-34. Thus, we find the written description requirement also is satisfied for claims 1-2, 6, and 27-34.

CONCLUSION

In summary, we affirm the § 103(a) rejection of claims 1 and 30, and reverse the § 112, ¶ 1 rejection of claims 1-2, 6, and 27-34 based on lack of written description.

Pursuant to § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 2, 6-7, 28, and 31-34 under § 103(a), as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

ADAMS, *Administrative Patent Judge*, dissenting.

I disagree with the majority's decision to affirm the rejection of claims 1, 2, 6, 7, 27-34 under 35 U.S.C. § 103. In my opinion, the evidence on this record lacks the necessary factual foundation to support this conclusion. Accordingly, I dissent.

Because the majority correctly finds that Appellants' Specification provides written descriptive support for claims 1-2, 6, and 27-34, I limit my discussion to the rejection under 35 U.S.C. § 103.

Overview:

The claims before us on appeal are drawn to a zinc finger polypeptide library wherein each polypeptide comprises more than one zinc finger (e.g., three zinc fingers[6]). "Zinc fingers, as is known in the art, are nucleic acid binding molecules" (Specification 6[7]: 23). The DNA binding portion of a zinc finger consists of an α-helix. The art has applied a numbering scheme for this α-helix, wherein the amino acid positions in the α-helix are numbered consecutively starting with the first amino acid of the α-helix as

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[6] While more than one zinc finger reads on at least two zinc fingers, the issue before this panel does not turn on the number of zinc fingers in each polypeptide. Therefore, I discuss the claimed zinc finger polypeptide library in the context of a library, wherein each polypeptide comprises three zinc fingers. I do so, because the prior art before this panel teaches zinc finger polypeptide libraries wherein each polypeptide comprises three zinc fingers (e.g., three finger libraries).

[7] For clarity, I note that the pages of Appellants' Specification have page numbers at both the top and bottom of the page. Unfortunately, the page numbers on any given page do not correspond to each other. Accordingly, I will refer to those page numbers that appear at the top of each page of Appellants' Specification.

+1 (*see, e.g.,* Choo '94-1 11164: col. 2, ll. 5-7). Accordingly, the -1 position represents the amino acid immediately preceding the +1 position.

It has been found that due to the consecutive turns in the α-helix of the zinc finger; positions -1, 3, and 6 of each finger make a specific contact with a single DNA strand (e.g., a first strand) at the 3' middle and 5' positions of a 3-base pair (bp) DNA target site (*see, e.g.,* Isalan 5617: col. 1, ll. 5-10; 5618: Fig. 1a). It has also been found that position 2 of the zinc finger may play a part in the recognition of DNA by binding the complimentary (e.g., second) DNA strand. Specifically, while positions -1, 3, and 6 make contact with the DNA target site and are considered to be the primary amino acid positions in the zinc finger α-helix; it has been found that with polypeptides comprising at least two zinc fingers, an auxiliary position, the 2 position of the preceding zinc finger may also be involved in the recognition of DNA (Choo '94-1 11166: col. 2, ll. 67-69; Choo '97 117: col. 2, ll. 36-42).

However, the contribution of this "auxiliary" 2 position of a zinc finger to DNA recognition and binding is less than clear. For example, Choo '94-2 report that "[t]he amino acid at position +2 is able to modulate or enhance the specificity of the amino acid at other positions" (Choo '94-2 11170: col. 2, ll. 9-11). This same group, however, reports that but for a specific instance when the -1 position is the amino acid Arg and the amino acid at the +2 position is Asp, any contacts this +2 position "might make with the second DNA strand do not contribute significantly to the stability of the protein-DNA complex" (Choo '94-1 11166: col. 1, ll. 15-19).

Nevertheless, to account for any possible effect the +2 position of a zinc finger may have on DNA recognition and binding, when a zinc finger polypeptide comprising at least two zinc fingers is considered, the DNA

binding site expands from 3-bp to 4-bp (Isalian 5618: col. 1, Fig. d; 5620: col. 2, ll. 37-40). In this regard, "[e]ach zinc finger binds to a quadruplet sequence in a target nucleic acid through contacts between specific amino acid residues of the α-helix of the zinc finger and the nucleic acid strand" (Specification 6: 23-26). Appellants explain that "[t]he quadruplets specified in the present invention are overlapping, such that, when read 3' to 5' on the –strand of the nucleic acid, base 4 of the first quadruplet is base 1 of the second, and so on" (Specification 6: 26-28; Fig. 1).

Recognizing that, in certain circumstances, there is an interrelationship between two adjacent zinc fingers of a zinc finger polypeptide, those of ordinary skill in the art have appreciated that the evaluation of zinc fingers is best performed in what is referred to as "context-dependent interactions," e.g., the interactions between neighboring fingers and DNA target sites (Greisman 657: col. 3, ll. 24-28). Therefore, the art before us on this record speaks of three finger libraries, e.g., libraries of zinc finger polypeptides that comprise three zinc fingers.

As outlined below, the work in this field has attempted to develop a set of rules through which one can predictably design a zinc finger polypeptide that will recognize and bind a particular DNA target site. The reports of this work in the literature, at the time Appellants' claimed invention was made, indicate that while some interesting observations have been made; there is still "no general code that can be used to design optimal zinc finger proteins for any desired target sequence or that can predict the preferred binding site of every zinc finger protein" (Greisman 659: col. 2, ll. 16-21; *see also* Choo '94-1 11167: col. 1, ll. 3-6 ("although sequence homologies are strongly suggestive of amino acid preferences for particular

base pairs, we cannot confidently deduce such rules until the specificity of individual fingers for DNA triplets is confirmed.")

The work in this field has led those of ordinary skill in the art to the conclusion that the zinc finger recognition code is a degenerate code (Choo '97 121: col. 1, ll. 7-8). In this regard, those of ordinary skill in the art have found that the structural conformation of the zinc finger itself; and more particularly, the α-helices contribute to the degeneracy of the zinc finger code (Choo '97 121: col. 1, ll. 8-15). In addition, those of ordinary skill in this art have found that "[a]lthough the zinc finger structure directly enables the binding mode that results in the possibility of coded contacts, we must emphasize that protein-DNA recognition is mutual and that DNA is, therefore, not a passive participant in the binding reaction" (Choo '97 124: col. 1, ll. 26-30).

Further complicating the attempts in the art to develop a code, or set of rules, that can be used to predictably design zinc finger polypeptides is the recognition that even when one selects a naturally occurring zinc finger polypeptide (e.g., Zif268) as a starting point - "natural DNA-binding sites for proteins are rarely the optimal binding sequences, and that naturally occurring proteins often evolve to recognize a variety of different binding sites" (Choo '97 123: col. 1, ll. 1-5).

Nevertheless, despite the foregoing hurdles that must be overcome in order to predictably design zinc finger polypeptides, those in the field remain optimistic that the degenerate zinc finger code will be cracked, so - the work continued.

Appellants now come before this panel with a disclosure of a library "in which randomization is limited to substituting amino acids which are known to dictate variation in binding site specificity" (Specification 3:1-3). According to Appellants'

> [t]he present invention provides a code of amino acid position bias which permits the selection of the library against any nucleic acid sequence as the target sequence, and the production of a specific nucleic acid-binding protein which will bind thereto. Moreover, the invention provides a method by which a zinc finger protein specific for any given nucleic acid sequence may be designed and optimized. The present invention therefore concerns a recognition bias which as been elucidated for the interactions of classical zinc fingers with nucleic acid. In this case a pattern of rules is provided which covers binding to all nucleic acid sequences.

(Specification 3: 23-30.)

Claim interpretation:

Claims 1 and 30 are the only independent claims of record. Claims 2, 6, 7, and 27-29 depend from claim 1; claims 31-34 depend from claim 30. The claims are drawn to a zinc finger polypeptide library. The claimed library is a composition, e.g., a product.

Notwithstanding the majority's supposition[8], as Appellants explain

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[8] In what they refer to as Finding of Fact #1, the majority asserts that a "'library' requires two polypeptides. (Spec. 3 [sic, 5] ('library is used . . . to denote a collection of polypeptides')" (*supra* 8). The majority's definition of the term "library" lacks the precision to which those of ordinary skill in the art would recognize the term to represent. Under the majority's definition a "library" would represent a composition consisting of two of the exact same polypeptides. This is not how a person of ordinary skill in the art would interpret this term.

> [t]he term "library" is used according to its common usage in the art, to denote a collection of polypeptides or, preferably, nucleic acids encoding polypeptides. The polypeptides of the invention contain regions of randomization, such that each library will comprise or encode a repertoire of polypeptides, wherein individual polypeptides differ in sequence from each other."

(Specification 5: 3-7.) Therefore, even if a library is construed to represent only two polypeptides, those two polypeptides must be in the same composition and must differ in sequence from each other to be considered a library.

The claimed zinc finger polypeptide library requires that each polypeptide of this library comprises more than one zinc finger (e.g., at least two zinc fingers; in the context of the prior art before us on this record - a library, wherein the zinc finger polypeptides have three zinc fingers). Each zinc finger comprises amino acid positions -1 to +9, wherein position 1 represents the first amino acid of an alpha helix. As discussed above, this numbering scheme is consistent with the numbering scheme used in the art.

If this was all Appellants' had claimed, the zinc finger libraries would be anticipated by any number of prior art references, e.g., Greisman. Appellants, however, have not claimed a generic zinc finger library. To the contrary, Appellants have claimed a very specific zinc finger library. More specifically, Appellants' library is defined by the process by which it is made.

The process that defines the claimed product:

According to Appellants' claims, the polypeptides of the claimed library are at least partially randomized, wherein the randomization[9] extends to cover at least positions 6 and 2 of adjacent first and second fingers. Therefore, at a minimum, claims 1 and 30 require that those amino acids at positions 6 and 2 of the adjacent first and second fingers respectively are randomized. Appellants' Specification discloses this concept as a preferred embodiment of the invention (Specification 9: 6-7 "[p]referably, each library will comprise randomisation . . . [of] at least position 6 of the first finger and position 2 of a second finger."). For clarity, the following illustration characterizes a three finger library, wherein the zinc finger polypeptides have amino acid positions -1 to 9. The box around positions 6 and 2 emphasize the adjacent relationship of the only two amino acids of this zinc finger polypeptide that are absolutely required, by the claims on appeal, to be randomized.

1st Finger 2nd Finger 3rd Finger

-1 1 2 3 4 5 [6] 7 8 9 -1 1 [2] 3 4 5 6 7 8 9 -1 1 2 3 4 5 6 7 8 9

The process does not end there. According to Appellants claims position 2 of the second finger and position 6 of the first finger are randomized with a specific set of eight amino acids. Specifically:

Claim 1 requires that the randomization of the amino acid residue at position 2 is restricted to amino acids selected from the group consisting of D, A, R, Q, H, K, S, and N.

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[9] According to Appellants the term "[r]andomisation, as used herein, refers to the variation of the sequence of the polypeptide which comprise the library, such that various amino acids may be present at any given position in different polypeptides" (Specification 5: 11-13).

Claim 30 requires that the randomization of the amino acid residue at position 6 is restricted to amino acids selected from the group consisting of R, Q, V, A, E, K, N, and T.

Summary:

The claimed zinc finger polypeptide library is a collection of zinc finger polypeptides (e.g. at least two zinc finger polypeptides) that differ in sequence from each other.

Each polypeptide in the library comprises at least two zinc fingers.

The amino acid sequences of the polypeptides in the library are at least partially randomized, but they must, at a minimum, be randomized at position 6 of the first finger and position 2 of the second finger. In addition, claims 1 and 30 set forth the following rules when randomizing the amino acids at positions 2 and 6:

According to claim 1, position 2 of the second finger must be an amino acid chosen from the group consisting of D, A, R, Q, H, K, S, or N. Position 6 of the first finger, however, can be randomized with any amino acid.

According to claim 30, position 6 of the first finger must be an amino acid chosen from the group consisting of R, Q, V, A, E, K, N, and T. In claim 30, position two can be randomized with any amino acid.

Issue:

The issue before this panel is whether the prior art, alone or in combination, teaches or suggests a zinc finger polypeptide library, wherein the amino acids residues at least at position 2 or 6 are randomized according

to the randomization rules set forth in Appellants' claims 1 and 30 respectively.

The Rejection of Record:

The claims stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Greisman and Choo '95.

Findings of Fact (FF):

i. Phe, Tyr, Trp, and Cys do not, or only rarely, appear in positions -1 to 8 of a zinc finger (Choo '94-1 11164: col. 2, ll. 45-49; Greisman 660 n. 15).

ii. Greisman teach a zinc finger library wherein positions -1, 1, 2, 3, 5, and 6 were randomized with codons that "allow 16 side chains at each position (all residues except Cys, Phe, Tyr, and Trp) . . ." (Greisman 658: Fig. 1, legend; 660: col. 1, n. 15). Stated differently, Greisman produced a zinc finger library, wherein positions -1, 1, 2, 3, 5, and 6 of each finger in the library where randomized with 16 different amino acids.

iii. Griesman report that "[a]ll phage display libraries contained between 5.6×10^8 and 1.9×10^9 clones" (Gresiman 660 n. 15).

iv. While conserved residues often appear at position -1, 3, or 6 of the α helix when adenine or guanine is present in the primary strand of one of Greisman's binding sites; Greisman found no such simple patterns at other positions in their selected proteins. Specifically, Greisman report that they "found no simple patterns of residues at positions 1, 2, and 5 of the α helix, and when thymine or cytosine occurs on the primary strand (Fig. 3), we found no simple pattern of potential contacts from residues at positions

-1, 3, and 6" (Greisman 659: col. 1, l. 33 - col. 2, l. 5).

v. At the end of Greisman's study, the authors report that "there still is no general code that can be used to design optimal zinc finger proteins for any desired target sequence or that can predict the preferred binding site of every zinc finger protein" (Greisman 659: col. 2, ll. 16-21).

vi. While Choo '95 reports that "[s]eventeen different triplets were used in successful selection experiments" and that "[t]he zinc fingers selected by a given triplet were found to have a bias towards a particular amino acid in three positions (-1, 3 and 6) . . ." (Choo '95 432: col. 1, ll. 32-36); Choo '95, does *not* identify which amino acids the triplets were biased towards.

vii. "In almost all of the selected fingers in which Arg recognizes G[uanine] at the 3' end, Asp occurs at position +2 to buttress the long Arg side chain . . ." (Choo '94-1 11166: col. 1, ll. 13-15; Choo '97 119: col. 2, ll. 14-18 ("[i]n certain cases . . . two amino acids from different positions appear to cooperate in specifying one base . . .; for instance, the buttressing interaction of position 2, aspartate, with position -1, arginine, which contacts guanine . . .").

viii. "When position -1 is not Arg, Asp rarely occurs at +2, suggesting that in this case any other contacts it might make with the second DNA strand do not contribute significantly to the stability of the protein-DNA complex" (Choo '94-1 11166: col. 1, ll. 15-19).

ix. "When adenine is present at the 3' end of a triplet, Gln is often selected at position -1 of the α-helix, accompanied by small aliphatic residues at +2. . ." (Choo '94-1 11166: col. 2, ll. 3-6).

x. "Thymine at the 3' end of a triplet selects a variety of polar amino acids at -1 . . . and occasionally returns fingers with Ser at +2 . . ." (Choo '94-1 11166: col. 2, ll. 34-38).

xi. Based on "[p]reliminary modeling studies" Isalan speculates that "histidine in position 2 might make a cross-strand contact to G[uanine] or T[threonine] while maintaining the buttress to Arg -1." (Isalan 5620: col. 1, ll. 10-14). In this regard, Isalan reports that "phage selections from randomized C-terminal finger libraries have yielded several fingers with His2, and Leu or Ser at position 1 . . ." (Isalan 5620: col. 1, ll. 14-18).

xii. "Gln at position -1, which is specific for adenine at the 3' end of a triplet when position +2 is a small nonpolar amino acid such as Ala but is specific for thymine when a polar residue such as Ser is at position +2" (Choo '94-2 11170: col. 2, ll. 2-5).

xiii. "The amino acid at position +2 is able to modulate or enhance the specificity of the amino acid at other positions" (Choo '94-2 11170: col. 2, ll. 9-11).

xiv. In a three finger library, "Asp at position +2 of finger 3 is dominant over the amino acid present at position +6 of the middle finger, precluding the possibility of recognition of adenine or cytosine at the 5' position" (Choo '94-2 11170: col. 1, ll. 52-56).

xv. With regard to the Zif268 zinc finger polypeptide binding domain,

> [t]he first and third fingers have positions: -1. arginine: 3. glutamate: and 6. arginine: and bind 5' -GCG-3'; whereas the middle finger has positions: -1. arginine: 3. histidine: and 6. threonine: and binds 5' -TGG- 3'. . . . Only one type of contact is observed to the second DNA strand, by position 2. aspartate,

> which contacts a cytosine found in the subsite of the preceding zinc finger . . . .

(Choo '97 117: col. 1, ll. 36-42.)

xvi. When present at the 5' or 3' end of a triplet, guanine selects fingers with Arg at positions +6 or -1 of the α-helix, respectively (Choo '94-1 11166: col. 1, ll. 2-5 and 8-10).

xvii. "Occasionally, guanine at the 5' end of a triplet selects Ser or Thr at +6 . . ." (Choo '94-1 11166: col. 1, ll. 7-8).

xviii. "When thymine is at the 5' end of a triplet, Ser and Thr are selected at +6 (as is occasionally the case for guanine at the 5' end)" (Choo '94-1 11166: col. 2, ll. 32-34).

xix. "The triplets ACG . . . and ATG . . ., which have adenine at the 5' end, also returned oligoclonal mixtures of phage, the majority of which were of one clone with Asn at +6" (Choo '94-1 11166: col. 2, ll. 10-13).

xx. "Asp is also sometimes selected at +3 and +6 when cytosine is in the middle . . . and 5' . . . position respectively" (Choo '94-1 11166: col. 2, ll. 18-20).

xxi. "[I]n order that Ala may pick out thymine in the triplet GTG, Arg must not be used to recognize guanine from position +6, since this would distance the Ala residue too far from the DNA . . ." (Choo '94-2 11171: col. 2, ll. 30-35).

xxii. "Guanine bases in our sites appear to prefer Arg at positions -1 and 6 . . . . Adenine bases appear to . . . prefer Gln at position -1 and, to some extent, at position 6" (Greisman 660 n. 20).

xxiii. When

> adenine or guanine occurs in the primary strand of one of our binding sites (the strand corresponding to the guanine-rich strand of the Zif268 site), there often is a conserved residue at position -1, 3, or 6 of the α helix that could form hydrogen bonds with this base . . .

(Greisman 659: col. 1, l. 20-26, endnote omitted.)

xxiv. "[I]t appears that the identity of an amino acid at any one α-helical position [e.g., the -1 position] is attuned to the identity of the residues at the other two positions [e.g., the 3 and 6 positions] to allow three base contacts to occur simultaneously" (Choo '94-2 11171: col. 2, ll. 27-30).

xxv. "[A]lthough sequence homologies are strongly suggestive of amino acid preferences for particular base pairs, we cannot confidently deduce such rules until the specificity of individual fingers for DNA triplets is confirmed" (Choo '94-1 11167: col. 1, ll. 3-6).

xxvi. Choo'97 points out that

> [o]ne physical complication that leads to a degenerate code is that the helical pitch of the α-helix that means that the three recognition positions do not fall on exactly the same face of the helix. Hence, the three base-contacting positions are not equidistant from the DNA, and residues at position 3 of the helix (which is closer to the DNA) need to be shorter than at either positions -1 or 6.

Choo '97 121: col. 1, ll. 8-15; *see also* Choo '94-2 11171: col. 2, l. 35 – 11172: col. 1, l. 6.)

xxvii. Choo '97 provides a code table that illustrates that a number of different amino acids can specify a particular base in the DNA binding site (Choo '97 121: col. 1, ll. 1-2; Fig. 5). This exact same code table appears in

Choo '94-2 (Choo '94-2 11170: col. 2, Fig. 2). Choo '97 caution, however, that this table

> should not imply that all combinations of amino acids will be effective. The amino acid used by zinc fingers to specify a particular base depends on the position of that base in the cognate triplet, and sometimes on its sequence in context of the triplet. The zinc finger recognition code is therefore a degenerate code.

(Choo '97 121: col. 1, ll. 3-8.)

Analysis:

The prior art before this panel teaches randomized three finger zinc finger polypeptide libraries. There is, however, no teaching or suggestion in any of this prior art, alone or in combination, that teaches a zinc finger polypeptide library that falls within the scope of the requirements set forth in Appellants' claimed invention.

Griesman produce a zinc finger library wherein positions -1, 1, 2, 3, 5, and 6 of each finger in the library are randomized with 16 different amino acids (FF ii). The only 4 amino acids that Greisman did not use where those four that the prior art recognized did not, or only rarely, appear in positions -1 through 8 of known zinc fingers (FF i).

Griesman report that "[a]ll phage display libraries contained between 5.6×10^8 and 1.9×10^9 clones" (FF iii). Griesman report that after "multiple rounds of selections (Fig. 2) were completed, the final phage pools [(libraries)] bound tightly to their respective target sites [(e.g., the TATA box, p53 binding site, the nuclear regulatory element)]. DNA sequencing of *eight clones* from each *pool* [(e.g., sublibrary)] revealed marked patterns of

conserved residues (Fig. 3) . . ." (Greisman 658: col. 2, 1. 1 to col. 3, l. 3, emphasis added).[10] Greisman report the sequencing data of the eight clones selected from each screen in Fig 3 (Greisman 659: Fig. 3). The data listed in Fig. 3 is simply a listing of the deduced amino acid sequences of clones isolated from a zinc finger library. There is no indication in Greisman that the sequence of any of these clones is representative of all the polypeptides in the library, or the sublibraries of zinc fingers having specificity for one of the DNA target sequences. More specifically, there is no indication in Greisman that the amino acids at position 2 or 6 of these clones are representative of the amino acids at position 2 or 6 in the remaining polypeptides of the library or sublibrary. Given that Greisman generated libraries by randomizing positions -1, 1, 2, 3, 5, and 6 with 16 different amino acids in each position (FF ii), there is no reasonable expectation that the library, or any of the sublibraries, would be expected to contain only those zinc finger polypeptides that fall within the scope of Appellant's claims. Stated differently, there is no suggestion or teaching in Greisman of a library within the scope of Appellants' claimed invention.

There is also no teaching or suggestion in Greisman that when a randomized zinc finger polypeptide library is produced, the choice of amino acid at any given position in the zinc finger polypeptide should be reduced or restricted. There is no teaching or suggestion in Greisman that position 2 of the second finger, or 6 of the first finger, of a zinc finger polypeptide

[10] To dispel a myth that appears to have, at least inferentially, clouded both the Examiner's and the majority's reasoning; the clones that were selected for sequencing and reported in Fig. 3 of Greisman are *not* a library. They are individual clones – single polypeptides.

should be randomized only with the specific amino acids set forth in Appellants' claimed invention.

To the contrary, while Greisman find that under certain circumstances, a pattern may be found for positions -1, 3, and 6; there was no "simple patterns of residues at positions 1, 2, and 5 of the α helix . . ." (FF iv). In all, Greisman teaches a person of ordinary skill in the art that "there is no general code that can be used to design optimal zinc finger proteins for any desired target sequence or that can predict the preferred binding site of every zinc finger protein" (FF v). Therefore, it cannot be said that Greisman would have taught or suggested a zinc finger library within the scope of Appellants' claimed invention.

Choo '95 does not make up for the deficiencies in Greisman. Choo '95 states that they observed that "zinc fingers selected by a given triplet were found to have a bias towards a particular amino acid in three positions (-1, 3 and 6) . . ." (FF vi). Choo '95, however, provides no description of these triplets or the particular amino acid that these triplets reportedly preferred. Having failed to suggest a preference for any particular amino acid at an position in the zinc finger it cannot be said that Choo '95 would have taught or suggested a zinc finger library within the scope of Appellants' claimed invention.

On reflection, the facts on this record establish that neither Greisman nor Choo '95 teach or suggest a library that falls within the scope of Appellants' claimed invention. Accordingly, I would reverse the rejection of claims 1, 2, 6, 7, and 27-34 under 35 U.S.C. § 103 as being unpatentable over the combination of Greisman and Choo '95.

The Examiner's position:

The Examiner directs attention to Greisman's Fig. 3, in an attempt to demonstrate that Greisman's teachings would have lead a person of ordinary skill in the art to produce a zinc finger library wherein the amino acid residue at position 2 or 6 is randomized with the restricted population of amino acids set forth in Appellants' claimed invention (Answer 10). According to the Examiner, Greisman's Fig. 3A illustrates that the 2 and 6 positions of the 4th Finger 1 sequence are "N", the 2 position of the 6th-8th Finger 2 sequences are "A", and the 6 position of all the Finger 2 sequences are either Q or A (Answer 10). From this the Examiner concludes that the sequences set forth in Fig. 3A "meet the claimed library with at least position 2 being a random residue at one finger and the adjacent finger with 6 having a random residue" (*id*). Based on this reasoning, the Examiner concludes that "the claimed library with the random amino acid residues includes or encompasses the library of random peptide of Greisman for each of the different fingers" (*id.*).

There are two problems with the Examiner's reasoning: First, as discussed above, the sequences illustrated in Greisman's Fig. 3 are of isolated clones – single polypeptides. These clones are not a library. Second, the Examiner's use of the phrase "includes or encompasses" suggests that the Examiner is of the opinion that as long as one of the amino acids listed in Appellants' claims for position 2 or 6 is found in a zinc finger polypeptide library, that library will read on the claim. This rationale is incorrect. According to Appellant's claims, the library is *restricted* to the amino acids "selected from the group consisting of . . ." (*see* claims 1 and 30). Stated differently, Appellants' claimed library is *restricted* to contain

only those zinc finger polypeptides that contain the amino acids listed in claims 1 and 30 at position 2 of the second finger and position 6 of the first finger respectively. Neither Greisman nor Choo '95 teach such a restricted library; nor do they suggest restricting the randomization of a zinc finger library in the manner set forth in Appellants' claims.

For the foregoing reason, I am not persuaded by the Examiner's rationale. The Examiner fails to adequately explain on this record why a person of ordinary skill in the art would have been lead to Appellants' claimed library based on the teachings of Greisman and Choo '95.

I recognize the Examiner's assertion that "[i]t would be within the ordinary skill in the art at the time the invention was made to pick and choose from the known available sixteen amino acids disclosed by Greisman, the ones that can combine to form the instant library." Stated differently, since Greisman teaches the randomization of positions -1, 1, 2, 3, 5, and 6 of each finger in the library with 16 different amino acids (FF ii); it would have been obvious to look at Appellants' claims and Specification, and select the same amino acids that Appellants selected. This assertion is the epitome of hindsight. As set forth in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007),

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))).

> I recognize the Examiner's assertion that
>
> > Greisman discloses, or at least suggests, from the 16 amino acids the random species at each positions [sic] of the zinc finger as shown at Fig. 3. Some of the combination of amino acids includes a random residue at positions 2 and 6, which is encompassed by the instant random residues at said positions. Gresiman [sic] teaches that each of the amino acids in the zinc finger is random amino acid that can be selected from 16 amino acids and discloses some specific ones.

(Answer 10-11.) As best as I can understand it, the Examiner seems to be asserting that since Greisman teaches that some of the amino acid residues at positions 2 and 6 of the representative clones set forth in Fig. 3 are the same as those set forth in Appellants' claims a person of ordinary skill in the art would have found it to have been prima facie obvious at the time Appellants' invention was made to select only those that would have met the requirements of Appellants' claimed invention. The problem is, however, that there is no evidence on this record that leads to this conclusion. Particulary, when Greisman states that no preferences were found for any position in a zinc finger (FF v).

On reflection, I note that in rejecting claims under 35 U.S.C. § 103, the Examiner bears the initial burden of presenting a prima facie case of obviousness. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). In this regard, "[t]he Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because *it* may *doubt* that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis." *In re Warner*, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967).

Where, as here, the Examiner fails to establish a prima facie case, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Accordingly, I would reverse the rejection of claims 1, 2, 6, 7, and 27-34 under 35 U.S.C. § 103 as being unpatentable over the combination of Greisman and Choo '95.

The majority opinion:

Notwithstanding the foregoing discussion, the majority picks up where the Examiner left off. According to the majority, "Appellants' elimination of 50% of the amino acids in a specific single position of a zinc finger in a zinc finger polypeptide was 'the product not of innovation but of ordinary skill and common sense' . . ." (*supra* 16). This is nonsense. Other than recognizing that work was being performed in this field[11], the majority makes no factual finding to support their position.

Nevertheless, to fill in the gaps of their factually deficient reasoning, the majority injects the legal concepts set forth in *Petering* and *Boesch*. These legal concepts fail to fill these gaps.

Petering:

According to the majority, here, "as in *Petering*, one of ordinary skill in the art would 'envisage *each member*' of the genus, including the 8 found in Appellants' subgenus" (*supra* 14). The majority's analysis is off base.

In reaching its conclusion, the *Petering* court noted that, while the generic formula in Petering was quite broad, "specific preferences" were described in the prior art. *Petering*, at 681, 133 USPQ at 279. Based on those disclosed preferences, the court found that the narrowed generic

[11] *See supra* 9: ¶ 8 through 10: ¶ 14; 11: ¶ 22; and 12: ¶ 27 through 13: ¶ 31.

formula essentially disclosed a limited class of approximately twenty compounds. Each was held to have been disclosed by the genus. *Petering*, at 681-682, 133 USPQ at 279-280.

In contrast to *Petering*, the evidence before this panel fails to provide a reasonable expectation that there is a preference for any particular amino acid at position 2 of a second zinc finger or position 6 of a first zinc finger (FF iv, v, xxv, and xxvii). At best, the evidence before this panel suggests that any observed preference reported in the art is preliminary and that before any rule based on an observed preference can be confidently deduced the specificity of individual fingers for DNA triplets must be confirmed (FF xxv). Further, as Greisman expressly states, "there still is no general code that can be used to design optimal zinc finger proteins for any desired target sequence or that can predict the preferred binding site of every zinc finger protein" (FF v).

Contrary, to the majority's conjecture, the facts on this record do not support a finding that since the prior art zinc finger libraries were created with a limited genus of 16 amino acids at each position, a person of "ordinary skill in the art would 'envisage *each member*' of the genus, including the 8 found in Appellants' subgenus" for the two specific zinc finger positions set forth in Appellants' claims (*supra* 14). In my opinion, the evidence before this panel would not even suggest the production of a zinc finger polypeptide library wherein every position (or even positions -1, 1, 2, 3, 5, and 6) of the zinc finger polypeptide was limited to those specific 8 amino acids set forth in Appellants' claimed invention.

Instead, the factual evidence before this panel establishes that that the amino acids in the DNA binding position of a zinc finger protein interrelate

with each other (FF xxiv), they are specific for particular DNA sequences (FF xxvi), and they are constrained by the conformation of the zinc finger itself (FF xxv). The majority's conjecture notwithstanding, those of ordinary skill in the art reached the opposite conclusion (FF iv, v, and xxv-xxvii).

Having failed to clearly state what evidence they believe would have lead a person of ordinary skill in the art to select only those eight amino acids that are set forth in Appellants' claimed invention for position 2 of the second finger or position 6 of the first finger, I am not persuaded by the majority's reliance on *Petering*.

Boesch:

Apparently recognizing the deficiency in their *Petering* analysis, the majority takes a different tack. According to the majority, "[t]he choice of amino acids in zinc fingers is a result-effective variable known to influence their binding to DNA" (*supra* 14). This is true and is, in fact, what all of the references before this panel teach. The problem with this analysis, however, was that nobody knew which amino acids at any given position of a zinc finger could be optimized by routine experimentation to lead to a predictable result. That is why those of ordinary skill in this art randomized the relevant positions of their zinc finger libraries with sixteen amino acids; excluding only those four that they knew did not, or only rarely, appear in the relevant portion of the fingers (FF i).

A conclusory statement is not sufficient to support a finding of obviousness - even under that guise of "routine optimization." As discussed above, the prior art provides no preferences that would lead to such a

conclusion. To the contrary, as discussed above, the prior art points in the opposite direction – that there are no preferences and therefore no reasonable expectation that a zinc finger polypeptide library could be "optimized" by restricting the number of amino acid choices at position 2 or 6, or any other position.

This concept of the obviousness of discovering optimum or workable ranges by routine experimentation was addressed in *In re Yates*, 663 F.2d 1054, 1056 n. 4, 211 USPQ 1149, 1151 n. 4 (CCPA 1981). In *Yates* the court found that in many instances it is true that it may be obvious to discover optimum or workable ranges by routine experimentation. The *Yates* court noted, however, that the problem

> with such "rules of patentability" (and the ever-lengthening list of exceptions which they engender) is that they tend to becloud the ultimate legal issue-obviousness-and exalt the formal exercise of squeezing new factual situations into preestablished pigeonholes. Additionally, the emphasis upon routine experimentation is contrary to the last sentence of section 103.

Stated differently, "it is facts appearing in the record, rather than prior decisions in and of themselves, which must support the legal conclusion of obviousness under 35 U.S.C. § 103." *In re Cofer*, 354 F.2d 664, 667, 148 USPQ 268, 271 (CCPA 1966); *Ex parte Goldgaber*, 41 USPQ2d 1172, 1176 (BPAI 1995) ("each case under 35 U.S.C. § 103 is decided on its own particular facts.")

While the majority relies on *Boesch* to support their "optimization" argument (*supra* 15), I note that the holding in *Boesch* was based a critical review of the evidence on that record and specific factual findings that lead the court to conclude that "the prior art would have suggested 'the kind of

experimentation necessary to achieve the claimed composition . . .'" *Boesch*, at 276, 205 USPQ at 219. On this record, the majority has done neither. Accordingly, I am not persuaded by the majority's unsupported conjecture.

KSR:

Nevertheless, just in case no one buys into their *Petering* or *Boesch* analysis, the majority leaps to *KSR*, asserting that "it's now apparent 'obvious to try' may be an appropriate test in more situations than we previously contemplated" (*supra* 15). According to the majority the reasoning in *KSR* "is applicable here" because,

> [w]hen there is motivation
>
> > to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

(*supra* 15-16.)

No doubt there was a problem to be solved - every prior art reference before this panel was interested in the same problem - how does one *predictably* design a zinc finger polypeptide to bind a particular DNA sequence. There was, however, *no* identified solution to this problem in the prior art, let alone no "finite number of identified, predictable solutions". To the contrary, rather than identify predictable solutions for the design of zinc finger polypeptides, the prior art expressly states that none exist (FF iv, v, and xxv). In addition, the prior art emphasizes that the complexity of this

system has frustrated the identification of predictable solutions (FF iv, v, and xxvi-xxvii). Accordingly, it is my opinion that the evidence before this panel fails to support a conclusion that Appellants' invention is obvious because it may have been "obvious to try."

Not to worry, the majority pulls another case out of their hat to address this pesky "predictability" issue. According to the majority,

> to the extent selection was "unpredictable," as Appellants argue (Reply Br. 8), unpredictability cannot be equated to nonobviousness when only a finite number of choices are available, as is the case here. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364, 82 USPQ2d 1321, 1332 (Fed. Cir. 2007) ("obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success").

(*Supra* 15.) As I understand the majority's reasoning, since they believe tere were only a finite number of choices and a reasonable probability of success there is no unpredictability in this art. For the reasons set forth above, the art does not support this conjecture, and in fact, those of ordinary skill in this art expressly teach the opposite (FF iv, v, and xxv-xxvii).

In addition, in *Pfizer* the Court noted that their conclusion was based on the particular *facts* in that case and on those *facts* the Court found that the prior art provided "ample motivation" to narrow the genus of 53 compounds to a few. *Pfizer*, at 1363-64, 1367, 82 USPQ at 1332-33. On this record, and in contrast to *Pfizer*, the majority makes no particular factual findings to support their conjecture. In this regard, I direct attention to *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, --- F.3d ---, 83 USPQ2d 1169, 1176-77 (Fed. Cir. 2007), for a discussion of the need to draw conclusions from the facts appearing in the record, rather than prior decisions in and of

themselves, particularly in the context of *KSR* and *Pfizer* as relied upon by the majority on this record.

For the foregoing reasons, I find the majority's conclusion that "[t]he skilled artisan would have had reason to use these methodologies [that were known in the art] to narrow the number of amino acids from 16 to 8 . . ." (*supra* 16) is wholly unsupported by the factual evidence on this record. The same is true of their assertion that "Appellants' elimination of 50% of the amino acids in a single position was 'the product not of innovation but of ordinary skill and common sense . . ." (*id.*).

In all, the majority has built a house of cards on the foundation of nothing more than random excerpts of the prior art and the "per se" application of so-called "rules of patentability." In my opinion, the majority's card house cannot stand up to the weight of the evidence on this record which expressly points in a direction that is opposed to the majority's conclusion. Therefore, contrary to the majority's conjecture, I find that the evidence before this panel is not sufficient to support a conclusion that Appellants' claimed invention would have been prima facie obvious over the combination of Greisman and Choo '95, alone or in combination with any of the other references relied upon by the majority.

Claim 30:

Lastly, the majority asserts that the library of claim 30 "is fully disclosed be [sic] Greisman" (*supra* 16). Apparently, the majority is of the opinion that the sequence of eight clones set forth in Fig. 3A of Greisman that were isolated from a library of between 5.6×10^8 and 1.9×10^9 clones,

or even a "sublibrary" of this larger library that was screened against the TATA box, is representative of the entire library or sublibrary. Neither Greisman, nor any other reference before this panel, support this assertion. For their part, the majority fails to support this assertion with a direct citation to that portion of Greisman that supports their position. Accordingly, I am not persuaded by their assertion that Greisman anticipates claim 30.

lbg

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